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Characterizing Uncertainty in RfDs and RfCs

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Traditionally, the determination of RfDs and RfCs has been conducted using deterministic approaches, resulting in a single value estimate. During the last decade, a number of investigators have sought to replace conventional default uncertainty factors with a distribution (the probability density function, or PDF) that characterizes the uncertainty in the size of a "true but unknown" scaling factor (e.g., Baird et al., 1996; Slob, 1997; Price et al., 1997; Swartout et al., 1998). These scaling factors are necessary to convert the observed end point to the "NOAEL in sensitive humans." One approach is to estimate the PDF by determining the ratio (e.g., of a subchronic to chronic NOAEL) for a reasonably large sample of chemicals, and then to assume that the chemical is a random member of the universe of chemicals. Other approaches include referring to toxicological "first principles," or toxicological "experience." In addition, certain investigators have attempted to address the uncertainty in the NOAEL (e.g., Leisenring and Ryan, 1992). Since the RfD and RfC are meant to be high confidence estimates of the "NOAELs in sensitive humans," the current RfDs and RfCs can be interpreted as lower bounds to the PDFs of the RfDs or RfCs. The RfDs and RfCs can also be viewed as the distributions of the uncertainty in the estimates of the population threshold doses. A probabilistic RfD has been developed for methylmercury (Clewell et al., 1999), based on a distribution of the input variables to the PBPK model used to convert hair mercury concentrations to a chronic intake rate.

Despite these efforts, there has been no systematic attempt to develop PDFs for existing RfDs and RfCs on IRIS. PDFs provide useful information for risk characterization and risk management, including (1) the disclosure of uncertainty, protectiveness and relatedness of a RfD/RfC to its PDF; (2) an opportunity for integration of uncertainty in dose response and exposure assessments, and (3) identification of the uncertainty in the estimates of RfDs for different compounds. While initial steps have been made towards developing PDFs for RfDs and RfCs, a number of issues remain. Work to date has not considered in detail how to take into account chemical-specific information in the development of the PDFs. For example, how does the PDF change if a reduced uncertainty factor (e.g., a factor of 3) is used to develop RfDs and RfCs, based on a consideration of the data? Conversely, should the "default" PDF be used if an uncertainty factor of 10 was used, not as a default, but because chemical-specific information supported a value larger than 3? How can uncertainty in the NOAEL and uncertainty in the UFs be combined into an overall PDF for the RfD/RfC? Proposals are sought for projects that address these issues, as well as other work to further the development and use of probabilistic RfDs/RfCs.

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